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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/674,935	HIRST ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,39,41,42,44,49,51,52 and 54-68* is/are pending in the application.

4a) Of the above claim(s) *65-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,39,41,42,44,49,51,52 and 54-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 15, 2008 has been entered.

Amendment Entry

2. The amendment filed October 15, 2008 has been entered. Claims 38, 41, 44, 49, 51 and 54 have been amended. Claims 1-37, 40, 43, 45-48, 50 and 53 are cancelled. Claims 65-68 have been newly added.

Election/Restrictions

3. Newly submitted claims 65-68 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The application contained inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1. The attorney of record elected without traverse, the invention drawn to stimulating an immune response; rather then the invention drawn to preventing or treating a disease, and similarly producing protective immunity.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 65-68 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims 38-39, 41-42, 44, 49, 51-52 and 54-64 are under consideration in this office action.

Withdrawal of Rejections and Objections

5. The following rejections and objections have been withdrawn in view of applicants' amendments and arguments:

a) The rejection of claims 38-39, 43-44, 49, 54-56 and 60-61 under 35 U.S.C. 102(b) as being anticipated by Williams et al., (WO 97/02045 published January 23, 1997);

b) The rejection of claims 38-44, 46-47, 49-52 and 54-64 under 35 U.S.C. 102(b) as being anticipated by Hazama et al., (Immunology, 1993); and

c) The objection of claims 38 and 40-42 under 37 CFR 1.75(c).

Response to Arguments

6. Applicant's arguments with respect to claims 38-39, 41-42, 44, 49, 51-52 and 54-64 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Rejection Necessitated By Amendments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 38-39, 41-42, 44, 49, 51-52 and 54-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al., (WO 97/02045 published January 23, 1997) in view of Hazama et al., (Immunology, 1993).

Claim 38 is drawn to a method of enhancing a lymphocyte mediated or immunoglobulin mediated immune response against an infectious disease, in a mammal in need thereof, comprising co-administering to the mammal a therapeutically effective amount of *Escherichia coli* heat labile enterotoxin B subunit (EtxB), an antigen, wherein the EtxB is free from whole toxin and is not linked to an antigen, wherein the antigen is a virus antigen from the herpes virus family, wherein the combination of ExtB and antigen are a vaccine and wherein the enhancement is compared to a lymphocyte mediated or immunoglobulin mediated immune response to the vaccine against an infectious disease compared to the lymphocyte mediated or immunoglobulin mediated immune response to the vaccine against an infectious disease after administration of the vaccine alone.

Claim 49 is drawn to a method of enhancing a B and T cell lymphocyte mediated or immunoglobulin mediated immune response to a vaccine against an infectious disease, in a mammal in need thereof, comprising administering *Escherichia coli* heat labile enterotoxin B subunit (EtxB) in conjunction with administration of an antigen associated with an infectious disease, wherein the EtxB is free from whole toxin and is not linked to the antigen, to the mammal in an amount which is effective to increase the mammalian subject's levels of B and T cell lymphocyte response to the antigen, wherein the combination of ExtB and antigen are a vaccine, wherein the antigen is a virus antigen from the herpes family, and wherein the enhancement is compared to a lymphocyte mediated or immunoglobulin mediated immune response to the vaccine against the infectious disease after administration of the vaccine alone, thereby enhancing the B and T cell lymphocyte mediated or immunoglobulin mediated immune response to the vaccine against the infectious disease compared to the lymphocyte mediated or immunoglobulin mediated immune response to the vaccine against the infectious disease after administration of the vaccine alone.

Claim 54 is drawn to a method of generating a lymphocyte mediated or immunoglobulin mediated immune response, in a mammal in need thereof, comprising administering to the mammal between 50 and 100 ug of subunit EtxB, wherein the EtxB is free from whole toxin and an antigenic determinant, wherein the EtxB and antigenic determinant are not linked to form a single active agent.

Claim 60 is drawn to a method of enhancing a B and T cell lymphocyte mediated or immunoglobulin mediated immune response, in a mammal in need thereof,

comprising administering between 50 and 100 ug of EtxB in conjunction with administration of an antigenic determinant associated with an infectious disease, wherein the EtxB is free from whole toxin and is not linked to the antigen, and wherein the EtxB and antigenic determinant are not linked to form a single active agent.

Claims 57 and 62 are drawn to the antigen is a virus antigen from the herpes virus family. Claims 41, 51, 58 and 63 are drawn to the virus antigen being selected from the group consisting of Herpes Simplex Virus- 1 (HSV- 1), Herpes Simplex Virus-2 (HSV-2), Epstein-Barr Virus (EBV), Varicella-zoster Virus (VZV), Cytomegalovirus (CMV), Human Herpes Virus-6 (HHV-6), Human Herpes Virus-7 (HHV-7) and Human Herpes Virus-8 (HHV-8). Claims 42, 52, 59 and 64 are drawn to the virus antigen being selected from the group consisting of HSV- 1, HSV-2, CMV or EBV.

Claims 55 and 61 are drawn to the method wherein the EtxB and antigenic determinant are administered to the mammal in need thereof in multiple doses. Claim 44 is drawn to the EtxB and antigen being administered to the said mammalian subject in an amount which is effective to increase the mammalian subject's levels of B and T cell lymphocyte response to the antigen. Claims 39 and 56 is drawn to the EtxB increasing the levels of B and T cell lymphocyte response.

Williams et al., teach therapeutic agents for use in the treatment of mammalian diseases (page 1, line 35 – page 2, line 2). The basis of the invention is that the pure B-subunit of *E.coli* heat labile enterotoxin (ExtB) binds to receptors found on the surface of

mammalian cells and this binding induces differential immune response effects on lymphocytes including activation of B and T cells (page 2, lines 1-5). The acronym ExtB means the pure B subunit of *E.coli* heat labile enterotoxin (page 1, lines 34-36). Williams et al., teach co-administration of the therapeutic agent, which is ExtB and the antigenic determinant, thereby teaching separate administration of the moieties (pages 3-4, lines 5-3). Williams et al., teach the ExtB as a vaccine carrier because of its ability to modulate lymphocyte populations (page 10, lines 9-13). Williams et al., teach the agent is capable of modulating the immune response when delivered together with an unrelated foreign antigenic determinant and the antigen and agent are delivered together as separate moieties (page 10, lines 22-33). Williams et al., teach co-administration and separate administrations which occur at the same time (page 8, lines 7-13). Williams et al., teach that the wild type and mutant forms of ExtB have binding capabilities and are known as immunomodulators (page 11, line 31- page 12, line 5). Williams et al., teach the administration of EtxB or ExtB mutants to mice (page 14, lines 25-27). The results were expressed as mean IgG and IgA antibody titers in serum, wherein the results indicated an enhanced immune response by the antibodies, see Figure 2. Figure 3 teaches the kinetics of lymphocyte proliferation where the mice were injected with 30ug of a mutant version of ExtB (page 14, line 35- page 15 line 10). Williams et al., teach the injected amounts of ExtB are effective to enhance the level of the immune response. Figure 4 teaches that immunization with either pure or mutated ExtB caused an increased activation in B cells in the amount of 80ug/ml.

However, Williams et al., do not teach the virus antigen being from the herpes virus family.

Hazama et al., teach that the non-toxic B subunit (LTB) of the heat labile toxin produced by enterotoxigenic *Escherichia coli* has been expected to potentiate local IgA antibody response to co-administered foreign antigens (page 643 para. 2). The LTB of Hazama et al., is same B subunit of the heat labile *Escherichia coli* enterotoxin referred to by the instant claims as ExtB. Hazama et al., created a recombinant LTB (ExtB) and investigated the mouse mucosal and systemic immune response elicited by intranasal immunization with several forms of a recombinant viral antigen (page 644, para. 2). These immunizations included the use of truncated Herpes Simplex Virus Type 1 (HSV-1) glycoprotein D (t-gD) being co-administered with LTB (page 644, para. 2). Hazama et al., teach administering to the mammalian mouse subject an effective amount of the LTB wherein the LTB is free from whole toxin and not linked to an antigen. Hazama et al., teach co-administration. Hazama et al., also teach the measurement of the antibody response, see Table 1 (page 646), which shows the administration of effective amounts of LTB alone and the co-administration of t-gD and LTB. The LTB by itself exhibited high immunogenicity when administered (page 647, para. 2). Table 2, at page 646, shows protection against a HSV-1 challenge in mice while table 4 shows protective immunity against HSV systemic infection in mice. . However Table 2 is show that truncated glycoproteinD of HSV-1 co-administered with interleukin 2 (IL-2) and Table 4 shows t-gD linked EtxB. Table 1 clearly shows the co-administration of an HSV-1 antigen and the EtxB is free from whole toxin and not linked to an antigen. The

glycoproteins of HSV are vaccines against HSV-1 infectious agents, see the instant specification at example 1 (pages 33-34), example 4 (page 35), and example 7 (pages 36-37) which teach that these same HSV-1 glycoproteins are vaccines against HSV infections. Hazama teach mucosal and systemic antibody, i.e, immunoglobulin mediated immune response elicited by immunization. Hazama et al., teach co-administration and states that tgD-LTB co-administered with LTB produced a 10-fold level higher level of serum antibodies (page 648).

Therefore, it would have been prima facie obvious at the time of applicants invention to modify the method of enhancing a lymphocyte mediated or immunoglobulin mediated immune response against an infectious disease in a mammal comprising administering EtxB and an antigen as taught by Williams et al., wherein the modification includes the antigen being from the herpes virus family as taught by Hazama et al., in order to provide enhanced immunoglobulin mediated immune response elicited by co-administration of ExtB and an antigen from the herpes virus family which produced a 10-fold level higher level response. No more than routine skilled would have been required to prepare the co-administered therapeutically effective EtxB and antigen when both Williams et al, and Hazama et al, teach enhancing a lymphocyte mediated or immunoglobulin mediated immune response against an infectious disease in a mammal comprising co administering or administration in conjunction with EtxB and a viral antigen to no only induce immune response effects on lymphocytes including activation of B and T cells but also provide protective immunity against a Herpes virus, as taught by Hazama et al. Furthermore, one of ordinary skill in the art would have had a

reasonable expectation of success in modifying the method of enhancement when only routine skill is required to exchange the antigen and use an alternative herpes virus antigen when the art already teaches EtxB potentiates local IgA antibody response to co-administered Herpes virus antigens.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. The new matter rejection of claims 38-39, 41-42, 44, 49 and 51-52 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons already of record.

The rejection was on the grounds that neither the specification nor originally presented claims provides support for a method of enhancing a lymphocyte mediated or immunoglobulin mediated immune response against an infectious disease, in a mammal in need thereof, comprising co-administering to the mammal a therapeutically effective amount of *Escherichia coli* heat labile enterotoxin B subunit (EtxB), an antigen, wherein the EtxB is free from whole toxin and is not linked to an antigen, wherein the antigen is a virus antigen from the herpes virus family, wherein the combination of ExtB and antigen are a vaccine and wherein the enhancement is compared to a lymphocyte mediated or immunoglobulin mediated immune response to the vaccine against an infectious disease compared to the lymphocyte mediated or

immunoglobulin mediated immune response to the vaccine against an infectious disease after administration of the vaccine alone. Thus, there appears to be no teaching of a method for enhancing the level of a leukocyte mediated immune response against an infectious agent.

Applicant has pointed to support for the amendments to in Figures 1-4 of the instant specification. However the Figures do not teach enhancing the lymphocyte mediated or immunoglobulin mediated immune response against an infectious disease compared to the lymphocyte mediated or immunoglobulin mediated immune response to the vaccine against an infectious disease after administration of the vaccine alone and co-administering the vaccine, thereby enhancing the lymphocyte mediated or immunoglobulin mediated immune response to the vaccine against an infectious disease compared to the lymphocyte mediated or immunoglobulin mediated immune response to the vaccine against an infectious disease after administration of the vaccine alone. It appears that the entire specification appears to fail to recite support for the newly recited method of enhancement. Therefore, it appears that there is no support in the specification. Therefore, applicants' assertions are not found persuasive and the rejection is maintained.

Conclusion

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645